EXHIBIT D

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Risk Factors for Failure of Transvaginal Sacrospinous Uterine Suspension in the Treatment of Uterovaginal Prolapse

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Background and Purpose: The purpose of this study was to elucidate the risk factors for failure of transvaginal sacrospinous uterine suspension (SSUS) in the treatment of uterine prolapse and to examine methods for controlling these risk factors.

Methods: Sixty patients with second degree uterine prolapse or greater were included in this 2-stage study, with 33 in the risk factor assessment and 27 in the clinical study of a modified treatment to eliminate identified risk factors. Patients were followed for at least 5 years. The first part of the study evaluated the risk factors for operative failure and the efficacy of the operative procedure. The second part of the study evaluated a modified treatment plan to eliminate risk factors identified in the first part of the study.

Results: The failure rate for those with an elongated cervix (3 of 4, 75%) and those with third degree uterine prolapse (3 of 4, 75%) was significantly higher than for patients without either of these risk factors (6.9%, 2/29) [$p = 0.007$]. Concomitant partial trachelectomy for those with elongated cervix significantly reduced the failure rate from 75% to 0% (0/7) [$p = 0.024$]. In the risk factor study, SSUS was successful in 84.8% (28/33) of patients. In the clinical study of modified therapy to prevent significant risk factors, the success rate was 96.3% (26/27).

Conclusions: This study found that an elongated cervix and third degree uterine prolapse were the 2 main risk factors for recurrent uterine prolapse after SSUS. Concomitant partial trachelectomy as an adjuvant treatment of SSUS for treatment of uterovaginal prolapse in patients with an elongated cervix significantly reduces the rate of failure in these patients.

Key words: Postoperative complications; Risk factors; Suture techniques; Urogenital surgical procedures; Uterine prolapse

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Transvaginal sacrospinous fixation of a prolapsed vaginal cuff was first proposed by Amreich in 1951.[1] Randall and Nichols treated 18 patients transvaginally with fixation of the vaginal apex to the right side of the sacrospinous ligament in 1971.[2] Since then, this procedure has been widely adopted. Our review of the literature found that the reported failure rate of the vaginal suspension ranged from 2 to 19% of patients.[3–8]

Traditional treatment for uterine prolapse is vaginal hysterectomy. In those patients with a desire to bear more children or who are not willing to undergo hysterectomy, treatment becomes a challenge for the gynecologist. In 1989, Richardson et al reported successful treatment of 5 young women with transvaginal fixation of the uterus to the sacrospinous ligament.[9] In 1993, Kovac and Cruickshank reported 5 pregnancies and successful vaginal deliveries in 19 patients who had been treated with sacrospinous uterosacral fixations.[10] However, there has been little investigation of the risk factors for failure of the vaginal cuff suspension or the uterine suspension in this procedure. This study investigated the risk factors for failed transvaginal sacrospinous uterine suspension (SSUS) and the effectiveness of elimination of the identified factors as a means of preventing this failure.

Methods

This prospective study was conducted from June 1990 to May 1991 and from July 1993 to December 1994 for surgical treatment and follow-up was ended in

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2003. A total of 60 patients with second degree uterine prolapse or greater were enrolled in the study. Eligibility for this study included symptomatic uterine prolapse of second degree or greater in either young patients desiring to preserve fertility or patients who were not willing to undergo hysterectomy. Uterovaginal prolapse was graded to the modified Baden-Walker's classification. Briefly, the first degree of prolapse was defined as a prolapse of the uterus to the level of the midvagina. The second degree was a prolapse of the uterus to the level of the introitus, and the third degree was a prolapse beyond the introitus.[11] Gynecologic examination was performed in the lateral position using a Sim's speculum during a Valsalva maneuver. Sonography of pelvis was performed on every patient. In order to facilitate investigation of the efficacy of the surgical procedure in the treatment of uterine prolapse, any patient with enterocele, enlarged corpus or pathologic changes identified on sonography or during surgery after the cul-de-sac had been opened was excluded from the study. Patients with increased intra-abdominal pressure such as obese patients, or patients with chronic obstructive pulmonary disease or chronic constipation were also excluded.

In this study, we hypothesized that elongation of the cervix and third degree uterine prolapse were risk factors for failed uterine suspension. To test this hypothesis, the study was divided into 2 parts. The first part evaluated risk factors for operative failure as well as the efficacy of the operative technique. From June 1990 to May 1991, a total of 33 consecutive patients participated in the first part of this study. Uterine depth was adopted as an indicator of cervical length. Uterine sounding with a uterine probe (Taiyu, Japan) was used instead of sonographic measurement, because of its greater ease and routine use both in the outpatient clinic and during surgery, and also because third degree uterine prolapse made it difficult to measure cervical length properly by sonography. Patients with pathologic changes of the uterus were excluded from the study to prevent confounding of depth of uterine sounding assessment and its relation to cervical length.

To confirm the uterine depth, the uterine cavity was sounded gently by a uterine probe with the anterior cervical lip grasped by a Martin tenaculum (Taiyu) during a clinic visit and again at the time of surgery. The mean of the 2 measurements was defined as the uterine depth. The incidence of operative failure and its relationship to uterine depth were calculated. A 2-year gap between the 2 parts of the study was employed in order to allow enough follow-up time for the first stage before the second stage was begun. The second part of the study was designed to examine the effect of eliminating the risk factors identified in the first part of the study. Patients with third degree uterine prolapse were excluded. Concomitant partial trachelectomy was performed on patients with an elongated cervix as identified by a uterine depth of 10 cm or more. The procedures in the second part of the study were performed from July 1993 through December 1994. A total of 27 patients were enrolled and follow-up for at least 9 years except for 1 patient in each group who was lost to follow-up during the fifth and seventh years, respectively.

In addition to urinalysis, urodynamic study, and X-ray urethrocystography, preoperative assessments included pelvic floor relaxation assessment with a Sim's speculum to evaluate the degree of uterine prolapse and sonography. Outpatient visits were scheduled every 3-6 months for the first 2 years after operation and every 1-2 years thereafter. The minimum follow-up period was 5 years (range, 5 to 10 years). All operations were done by a senior gynecologist. Fisher's exact test was used for statistical analysis of the relationship between categorical variables. A p value < 0.05 was defined as statistically significant.

Operative technique

The surgical procedure followed Richardson et al's procedure with some modifications.[9] Briefly, a longitudinal incision was made through the posterior vaginal wall and carried to the fornix of the vagina. The vaginal wall was then separated from the underlying fascia and muscle attachments by sharp dissection as in a posterior repair. The right sacrospinous ligament was then palpated, and the ipsilateral pararectal space was entered by blunt dissection. The sacrospinous ligament was exposed and a Deschamps ligature carrier inserted into the ligament with 2 no. 1 Ethibone sutures (Ethicon, UK) under direct vision at least 2 cm medial to the ischial spine. In order to identify the uterosacral ligaments as well as pathologic uterine changes such as adenomyosis and myoma uteri (which render patients unsuitable for conservative uterine suspension), the peritoneal cavity was entered routinely. The Ethibone suture on each site of the uterosacral ligament was secured on each side. By a pulley effect, the cervix was drawn up lateral to the surface of the sacrospinous ligament, and the sutures were tied. Before tying the sutures, anterior colporrhaphy for cystocele and Kelly plication for stress incontinence, if necessary, were performed. The posterior repair was then completed. In the second part of the study, patients who had a uterine depth of 10 cm or more received partial trachelectomy immediately after anterior colporrhaphy to reduce the uterine depth to 7 cm. The cervix was then repaired by Stumdorf tracheloplasty.[12] During this procedure

(tracheloplasty), the cervical os was kept open by placing a Hegar dilator in the cervix.

Results

Sixty patients took part in this study, 33 in the risk factor identification study and 27 in the risk factor elimination study. The average age was 45.1 ± 12.5 years and the parity was 3.6 ± 2.1. Eighteen patients (30%) were postmenopausal. In the risk factor study, 4 patients had third degree uterine prolapse and 1 of these also had a uterine depth of 12 cm. The remaining patients all had second degree prolapse. Four of the patients had a uterine depth of ≥ 10 cm. There was no significant difference in age, parity, menopausal status, and incidence of cystocele or rectocele between patients in the risk factor identification and risk factor elimination studies ($p > 0.05$). Of the 33 patients in the risk factor study, 28 (84.8%) had a successful repair. Recurrent prolapse was significantly related to uterine depth. When the uterine depth was 10 cm or greater, 75% (3 of 4) of the operations failed. This failure rate was significantly higher than in those with a uterine depth < 10 cm (6.9%, 2 of 29) [$p = 0.007$, relative risk = 10.88, Fisher's exact test] (Table 1). Procedures failed in 3 of 4 patients (75%) with third degree uterine prolapse. Of the 29 patients with second degree uterine prolapse, only 2 (6.9%) failed the procedure, a significantly lower incidence than in those with third degree uterine prolapse ($p = 0.007$, Fisher exact test). One patient, who experienced recurrent prolapse, initially had a third degree prolapse and an elongated cervix (uterine depth of 12 cm) [Table 2]. Thus, an elongated cervix and third degree uterine prolapse were identified as risk factors for failed SSUS. The failure rate for those patients who had either of these risk factors was 71% (5 out of 7), which was significantly higher than for those patients without any of these risk factors (0 of 26) [$p < 0.001$, Fisher's exact test].

In the risk factor elimination study, patients with third degree prolapse were considered unsuitable for the suspension procedure and were thus excluded. A total of 27 patients with second degree prolapse were studied. Seven of these had a uterine depth of 10 cm or more and underwent concomitant partial trachelectomy and none experienced recurrence (0 of 7). The failure rate in those patients who underwent concomitant partial trachelectomy (0%) was significantly lower than in those who did not undergo this procedure (75%, $p = 0.024$, Fisher's exact test). The success rate was 96.3% and only 1 procedure failed (Table 3). This patient had a uterine depth of 7 cm and second degree uterine prolapse. Recurrence of the prolapse was found 6 months after SSUS. No risk factor for recurrence could be identified in this patient.

Six patients who wanted to become pregnant spontaneously conceived (100%) and successfully delivered by cesarean section. Half of them had undergone partial trachelectomy. Five of these patients delivered at term and 1 who had a history of

Table 1. Recurrent uterine prolapse as related to uterine depth in the risk factor identification and risk factor elimination studies.

Uterine depth	Identification study	Elimination study	*p* value*
≥ 10 cm	3/4 (75%; RR† = 10.88)	0/7 (0%; RR‡ = 1.04)	0.024
< 10 cm	2/29 (6.9%)	1/20 (5%; RR§ = 0.73)	0.639
p value	0.007	0.741	

* Fisher's exact test.
† Estimated RR of failure in reference to patients with uterine depth < 10 cm in risk factor identification study by Fisher's exact test.
‡ Comparison of the RR between patients with uterine depth ≥ 10 cm undergoing concomitant partial trachelectomy in the risk factor elimination study and uterine depth < 10 cm in the risk factor identification study by Fisher's exact test.
§ Comparison of RR between 2 stages with uterine depth < 10 cm by Fisher's exact test.
RR = relative risk.

Table 2. Characteristics of patients with recurrent uterine prolapse.

Patient no.	Age (years)	Parity	Interval to recurrence	Uterine depth	Preoperative uterine prolapse	Postoperative uterine prolapse
1*	57	5	1 month	7 cm	Third degree	Second degree
2*	42	2	6 months	8 cm	Third degree	First degree
3*	36	3	4 months	10 cm	Second degree	First degree
4*	43	3	12 months	11 cm	Second degree	Second degree
5*	33	1	1 month	12 cm	Third degree	Third degree
6†	68	7	6 months	7 cm	Second degree	First degree

* Risk factor identification study.
† Risk factor elimination study.

Table 3. Recurrent uterine prolapse as related to uterine depth in risk factor elimination study.*

Uterine depth	No. of patients	Recurrence
6 cm	2	0 (0%)
7 cm	9	1 (11%)
8 cm	6	0 (0%)
9 cm	3	0 (0%)
10 cm	3	0 (0%)
11 cm	3	0 (0%)
12 cm	1	0 (0%)
Total	27	1 (3.7%)

* Concomitant partial trachelectomy was performed on those patients who had a uterine depth of 10 cm or greater as determined by uterine sounding with a uterine probe.

cervical incompetence delivered at 37 weeks. There was no recurrence of prolapse after cesarean section.

Discussion

There have been few studies of the failure rate of transvaginal uterine suspension by sacrospinous ligament fixation. Our risk factor study of 33 patients showed that the failure rate in those with an elongated cervix (75%) or third degree uterine prolapse (75%) was significantly higher than in those patients without these risk factors (6.9%) (both $p = 0.007$). Further study of these risk factors with a larger sample size was not justifiable. In the second part of this study which eliminated these risk factors, the recurrence rate was reduced from 15.2% (in the risk factor study) to 3.7%. There was no overlap between patients with elongation of the cervix and third degree uterine prolapse in the 4 out of 5 operative failures in the risk factor study, suggesting the independence of these factors.

SSUS failure is of great concern. The elongated cervix is usually in the middle of the vagina even after the suspension operation. This problem can be resolved by concomitant partial trachelectomy to restore the elongated cervix to its normal anatomic size and expected position after fixation operation. In patients with third degree uterine prolapse, the tension was quite high after the cervix was drawn up and tied to the surface of the sacrospinous ligament, resulting in a high failure rate. Although uterine prolapse basically occurs due to defects of support, it appears that the mechanism of failed surgical reconstruction for elongated cervix is different from that of uterine prolapse. Elongated cervix is commonly combined with uterine prolapse as was the case in 11 out of 60 (18%) patients in this series. If so, concomitant partial trachelectomy in these patients is a reasonable approach.

This study found that third degree uterine prolapse was a risk factor for operative failure in the treatment of uterine prolapse by SSUS. Vaginal hysterectomy with pelvic reconstruction may be an alternative treatment in these patients. The optimal management of patients with third degree prolapse who desire future childbearing remains to be determined. A surgical procedure which ensures satisfactory results for these patients has not been established. Third degree uterine prolapse is rare in young women with childbearing potential, especially in developed countries, which may limit the demand for these procedures.

In this series 30% of patients were postmenopausal. It is a common practice to recommend vaginal hysterectomy instead of uterine suspension for women who have completed childbearing. However, many women from Taiwan are resistant to the idea of removal of a normal uterus, either because of psychologic misgivings or for reasons related to body image. Some young women with uterovaginal prolapse prefer an operation that will allow continuous menstrual function even when additional pregnancies are not an issue.[13] Maher et al reported similar success rates of 72% in the hysterectomy group and 74% in the hysteropexy group for patients who had uterine prolapse ($p = 1.0$). Sacrospinous hysteropexy was effective in the treatment of uterine prolapse.[14] However, it still had a significant failure rate. For these reasons, it is important to identify factors that predict SSUS failure so that patients can be properly informed of the failure rate before operation.

For young patients who want to bear more children, the effect of reconstructive surgery on fertility potential is important. In 1933, Shaw reported that cervical amputation adversely affected the outcome of subsequent pregnancy.[15] The frequency of cervical dystocia, cervical lacerations, cervical incompetence, and premature birth was increased after the Manchester procedure. Cervical stenosis and infertility might also occur.[15–17] In our series, 6 patients, including 3 who had partial trachelectomy, desired more children. All conceived and carried their pregnancies to term without complications. The frequency of obstetric complications was not increased after SSUS with partial trachelectomy. This may be attributable to the restoration of the elongated cervix to normal anatomy in these patients. Also, because it avoids surgical manipulations of the tubes and ovaries, the transvaginal approach rarely results in pelvic adhesions that may cause infertility. With the help of assisted reproductive techniques, the association of cervical factors to infertility after concomitant partial trachelectomy can be effectively controlled. Further study of the effects of SSUS with partial trachelectomy on fertility potential and pregnancy complications in a larger sample is warranted.

In conclusion, SSUS is an alternative treatment for uterine prolapse with a satisfactory success rate. In women with symptomatic uterine prolapse desiring childbearing or uterine preservation, this study showed that SSUS is an effective means of maintaining normal anatomy and preserving fertility. Elongated cervix and third degree uterine prolapse appear to be risk factors for surgical failure. Patients with third degree prolapse should be advised against undergoing this procedure. Partial trachelectomy at the time of the uterine suspension, to restore an elongated cervix to its anatomic size and position appears to be a promising technique to avoid recurrent prolapse.

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